Journal of the American College of Cardiology
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Published by Elsevier Inc.

Vol. 46, No. 12, 2005
ISSN 0735-1097/05/$30.00
doi:10.1016/j.jacc.2005.04.068

Cardiac Resynchronization Devices

The Food and Drug Administration's Regulatory Considerations

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Cardiac resynchronization therapy (CRT) devices have been studied clinically since 1998, and have been on the U.S. market since the Food and Drug Administration (FDA) approval of the first product in 2001. Since that time, the FDA has approved many different models from three different manufacturers, representing the first and second generations of these products. All of these products have undergone the FDA pre-market approval process, which examines the safety and effectiveness of the devices for their intended use. Over the last several years, the FDA has adapted recommendations for CRT clinical trials based on an evolving understanding of what these devices can achieve. This paper will outline the dynamic nature of the FDA's approval process for CRT devices and briefly review the clinical trial designs for the first generation devices. (J Am Coll Cardiol 2005;46:2325–8) © 2005 by the American College of Cardiology Foundation

The U.S. Food and Drug Administration's (FDA) regulatory authority over medical devices extends to both their investigational use and market approval. The FDA's regulatory system is a risk-based system, with different requirements depending on the degree of risk posed by devices (Table 1). Pacemakers, implantable defibrillators, and cardiac resynchronization therapy (CRT) devices, therefore, are classified into the highest risk category, class III. These devices must meet stringent manufacturing controls and rigorous bench and animal testing and typically require clinical trials to fully evaluate device performance.

Regulations governing medical devices review and approval were modeled after the regulations established for drug approvals. Similar to drugs, devices must have a safety and effectiveness evaluation which supports an acceptable risk-benefit profile to gain approval. Manufacturing controls are considered as part of the review process, because it is through manufacturing controls that product consistency can be assured. Just as with drugs, individual devices are generally evaluated on a case-by-case basis. The FDA does not assume that devices are interchangeable across manufacturers; safety, effectiveness, and target population findings from a clinical trial evaluating one manufacturer's device may have limited applicability to another manufacturer's device.

Medical devices differ from drugs in that they may fail quickly, unpredictably, and late in their use. Physician technique, particularly for implantable devices, may strongly impact device performance and patient outcomes. Additional risks may occur through biologic incompatibility and interactions with other medical devices or equipment such as magnetic resonance imaging or other electromagnetic sources. Medical devices may even have a shorter market life than drugs. They are continually being modified to meet user needs, to improve manufacturing yields, or to correct deficiencies in design. The FDA's processes evaluate the incremental impact of these modifications on safety and effectiveness.

The FDA's understanding of CRT informs clinical recommendations for demonstrating safety and effectiveness. This understanding evolves by evaluating marketing applications, reviewing publicly available information, consulting with our advisory panel, and observing device performance and patient outcomes during the post-market period. Since the approval of the Medtronic (Minneapolis, Minnesota) InSync Biventricular Pacing System in 2001, the FDA has approved over two dozen CRT models from three different manufacturers. The first devices were evaluated in randomized blinded clinical trials comparing CRT-on to CRT-off (Table 2). The knowledge gained from these trials and subsequent field experience has allowed certain modifications to the approved technology to be fully evaluated based upon limited clinical data or bench testing alone.

CRT EFFECTIVENESS

Regarding effectiveness, FDA approval of medical devices requires that "there is reasonable assurance that a device is effective when it can be determined, based upon valid scientific evidence, that in a significant portion of the target population, the use of the device for its intended uses and conditions of use, when accompanied by adequate directions for use and warnings against unsafe use, will provide clinically significant results" (1). Thus, the data must support a clinically meaningful outcome in at least a patient subset.

In the first clinical trials, the FDA asked manufacturers to investigate whether CRT provided reasonable effectiveness

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Manuscript received April 13, 2005, accepted May 4, 2005.

JACC Vol. 46, No. 12, 2005
December 20, 2005:2325–8

Abbreviations and Acronyms

CRT = cardiac resynchronization therapy
EF = ejection fraction
FDA = Food and Drug Administration
ICD = implantable cardioverter-defibrillator
LV = left ventricular
NYHA = New York Heart Association

as an adjunct to optimal pharmacologic therapy for heart failure. Based on the FDA's understanding of the potential hemodynamic effect from CRT, early studies assessed exercise tolerance and quality of life in symptomatic patients.

The FDA convened its Circulatory System Devices Panel to interpret outcomes of trials for the first three applications for CRT: Medtronic's InSync (2), Guidant's (St. Paul, Minnesota) Contak CD (3), and Medtronic's InSync ICD (4). Experts in both heart failure management and electrophysiology focused on whether: 1) patients received standard optimal medical therapy, particularly beta blockers; 2) responder subgroups could be identified; and 3) the benefit was clinically meaningful across the population studied.

Panel concerns about bias from potential unblinding led to later recommendations for more objective endpoints such as peak oxygen consumption. Nevertheless CRT trials still include subjective measures such as quality of life, 6-min walk, and New York Heart Association (NYHA) function class because they are felt to be clinically meaningful.

CRT SAFETY

To meet the FDA's requirement for reasonable safety in a specific target population, manufacturers must provide "valid scientific evidence that the probable benefits to health from use of the device for its intended uses and conditions of use, when accompanied by adequate directions and warnings against unsafe use, outweigh the probable risks" (5).

In early clinical trials for CRT, the FDA evaluated conventional device- and procedure-related adverse events and data characterizing worsening heart failure such as number of heart failure hospitalizations, use of inotropes, and worsening symptoms.

Coronary sinus leads have presented unique acute and chronic safety concerns owing to a variety of lead shapes and fixation mechanisms. Trials have assessed lead safety through total procedure time, lead implant time, fluoroscopy time, lead implant success rate, and adverse events specifically associated with the lead (e.g., coronary sinus dissection, perforation, lead revisions, diaphragmatic stimulation, and dislodgements). The FDA recognized that physician experience and lead-related instruction strongly impacted safety and therefore mandated training as a condition of approval.

Table 1. Food and Drug Administration Classification of Medical Devices

Class	Examples
Class I	Manual stethoscope, cardiovascular surgical instruments
Class II	Vascular grafts (excluding coronary), biliary stents, PTA catheters
Class III	Pacemakers, implantable defibrillators, cardiac resynchronization devices, endovascular grafts, vascular stents, coronary artery bypass grafts, heart valves

Many CRT devices were originally developed on an implantable cardioverter-defibrillator (ICD) platform. In the U.S., most CRT devices now have this configuration, because the majority of CRT recipients are also candidates for an ICD. Concern that CRT could interfere with defibrillation was addressed in the clinical trials by secondary endpoints that confirmed ICD functionality.

Device reliability is a primary component of safety often better evaluated outside clinical trials. Bench tests are used to study rare events such as catastrophic failure, demonstrate appropriate levels of mechanical durability, biocompatibility, immunity from electrical noise, and hermeticity, and check standard measures of device safety. Bench testing of previous pacemakers and defibrillators provided the FDA with a valuable foundation in this regard.

INDICATIONS

The indications statement describes the population in whom a device is demonstrated to be safe and effective. Based on early clinical trials, currently marketed CRT devices are indicated for patients with low ejection fraction (EF), prolonged QRS duration and moderate to severe heart failure (NYHA functional class III/IV) despite stable, optimal medical therapy. Specific QRS durations and EFs were derived directly from enrollment criteria. However, the FDA's panel determined that sufficient benefit was not demonstrated for class II patients, so the NYHA functional class indication was subsequently limited. Importantly, the population the FDA indicates for a device may differ from that eligible for Center for Medicare and Medicaid Services reimbursement.

TOTAL PRODUCT LIFE CYCLE

The FDA's regulatory authority extends beyond the initial market approval of a device through post-market studies, supplemental applications for device modifications, and reporting of device problems.

Post-market studies. Post-market studies can be required by the FDA as a condition of approval. These studies provide information about long-term patient outcomes and device performance, which is not considered as necessary to make a pre-market approval decision but is nevertheless important to characterize. All original CRT device approvals have required a post-market study. The FDA's primary goal was to characterize outcomes beyond the six months of pre-market evaluation. These post-market studies were also designed to capture long-term electrical performance of the left ventricular (LV) leads. The FDA receives six-month updates regarding these studies. This information, in addition to other recent trial results (6,7), continues to shape the

Table 2. Primary Effectiveness End Points

Study Design	InSync (Medtronic)	InSync ICD (Medtronic)	Contak CD (Guidant)	Contak TR (Guidant)	Epic HF (St. Jude)
Year study began	1998	1999	1998	2000	2002
Year device approved	2001	2002	2002	2004	2004
Type of device	CRT-P	CRT-D	CRT-D	CRT-P	CRT-D
Comparison	CRT on vs. off	CRT on vs. off	CRT on vs. off	CRT on vs. off	CRT on vs. off
Follow-up	1, 3, 6 months	1, 3, 6 months	0, 3, 6 months	0, 3, 6 months	0, 1, 3, 6 months
Blinding	Double	Double	Double	Unblinded	Double
Primary effectiveness end point	NYHA functional class, 6-min walk, QOL*	NYHA functional class, 6-min walk, QOL*	Composite index (mortality, HF hospitalizations, therapy for VT/VF)	Peak V_{O_2}, 6-min walk†	Peak V_{O_2}
Additional effectiveness end points	Mortality, peak V_{O_2}, QRS, hospitalization, echo measures, neurohormones	Mortality, peak V_{O_2}, QRS, hospitalization, echo measures, neurohormones	Peak V_{O_2}, QOL, 6-min walk, NYHA functional class, echo measures, norepinephrine, heart rate	QOL and NYHA functional class	6-min walk, QOL, NYHA functional class, echo measures
Sample size (total randomized)	532	555	490	448	178

*The trial design defined success as occurring if any one of the three end points was statistically significant at alpha = 0.0167, if any two were significant at alpha = 0.025, or if all three were significant at alpha = 0.05. †The trial design defined success as occurring if: 1) peak V_{O_2} improved >0.7 ml/kg/min ($p < 0.05$) and 6-MWD improvement resulted in $p < 0.10$; or 2) peak V_{O_2} improved >0.5 ml/kg/min ($p < 0.10$) and 6-MWD improvement resulted in $p < 0.05$.

CRT = cardiac resyncronization therapy; HF = heart failure; NYHA = New York Heart Association; QOL = quality of life; VT/VF = ventricular tachycardia/ventricular fibrillation; V_{O_2} = oxygen consumption.

FDA's thinking and expectations for CRT device performance.

Device modification. Manufacturers propose device modifications when they seek to improve safety or effectiveness, expand utility, optimize manufacturing yields, or address post-market safety concerns. Following the least-burdensome approach, the FDA considers the incremental risks and benefits of device changes and identifies the types of evidence needed to characterize safety and effectiveness. When the potential clinical impact of changes can be well characterized through bench or animal testing, a clinical trial may not be required. When important clinical outcomes such as symptoms or mortality must be evaluated, or when the manufacturer wishes to expand the intended patient population for the device, a clinical trial is needed. New patient populations are reflected in the approved labeling for the device.

Recalls. Device recalls provide a way to link safety concerns from a variety of sources (including voluntary medical device reports) to coordinated action and recommendations by manufacturers and the FDA. Recent implantable pacemaker and defibrillator recalls have pertained to electrical circuitry abnormalities, battery and capacitor malfunctions, and anomalous behavior of firmware (8). If the correction involves a change to either the manufacturing process or the design of the device itself, a supplemental application to the FDA is required.

FUTURE DIRECTIONS FOR CRT DEVICES

Both CRT devices and their indicated populations evolve as the market for CRT expands. New technologies may allow physicians to better tailor therapy to the needs of particular patients or offer diagnostic enhancements that aid overall care. As new patient populations are investigated, the medical community may better understand who is most likely to benefit from CRT. Importantly, these studies may require new clinical endpoints better suited to their populations.

New CRT technologies. Since the first approvals, the medical community and industry have sought to optimize CRT by varying parameters such as electrode placement and stimulus timing. These pursuits have led to the development of devices that more flexibly deliver CRT. For example, some devices offer a variable delay between right and LV pulses. There has been considerable demand by clinicians for new lead designs which allow greater control over where stimulation is delivered. Critical to the implementation of these technologies, however, is an understanding of how to optimize cardiac function. Many questions remain about the relative importance of intraventricular and interventricular electrical and mechanical timing and their role in cardiac function and heart failure progression.

Although CRT device diagnostics are predominantly limited to electrophysiologic concerns such as battery life, pacing capture, or integrity of lead conduction, future devices will likely incorporate novel diagnostic measures that may help characterize the heart failure status of patients. While such features offer promise, their implementation presents new concerns, such as how such data would be presented to the physician and how those data should be interpreted, especially if traditional diagnostics are absent or contradict the device. Further, adequate specificity and sensitivity are needed to avoid unnecessary hospitalizations or interventions on the one extreme and misinformed complacency on the other.

New CRT populations. Although indications are not identical across manufacturers, most approved CRT devices are currently indicated for patients with moderate to severe heart failure (NYHA functional class III/IV) who have LV dysfunction and prolonged QRS duration and remain symptomatic despite stable optimal heart failure drug ther-

apy. It is unknown, however, whether CRT may benefit other heart failure populations and, if so, how such benefit should be assessed. For example, it is unknown whether CRT may help to slow or reverse the progression of heart failure in asymptomatic patients (NYHA functional class I/II) who have depressed LV function and prolonged QRS, patients with diastolic dysfunction and preserved EF, or patients who have contractile dyssynchrony but normal electrical timing. The risks and benefits of CRT will have to be demonstrated in these patients in order for a manufacturer to expand the indicated patient population for its device.

New clinical end points. The original pivotal CRT trials focused largely on exercise response and functional status. More recently, two large trials explored mortality and morbidity benefits (6,7). As trials target asymptomatic populations, however, alternative assessments of patient outcome may provide additional information. Some of the most promising parameters, such as those based on CRT-induced changes in systolic and diastolic dimension, may one day shed light into reverse remodeling. Generally assessed by echocardiography, these noninvasive measures may offer early and meaningful surrogates of heart failure progression and potential reversal if clinically meaningful standards for interpretation are developed.

CONCLUSIONS

Device-based therapies for heart failure are reviewed and approved by the FDA based on an evaluation of each device's safety and effectiveness. The FDA's approval of CRT devices hinges on a belief that these products are still a developing technology, and are primarily intended as an adjunctive therapy for patients on an optimal medical regimen. As clinical trials continue to explore responder groups and further our understanding of how patients benefit from these devices, the FDA's clinical trial recommendations will likewise evolve. Using this dynamic review process, the FDA will continue to meets its public health mission of ensuring safe and effective device therapies for heart failure patients.

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